Experience with Cortisone and ACTH in a Private Clinic

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SUMMARY

Cortisone and ACTH are valuable agents for treating a large variety of diseases. In appropriate situations they may save life. It may be possible to prevent loss of vision in eye disease or permanent damage to important viscera in generalized disease. With ready access to these agents through the pharmacist, it is important to know that cortisone and ACTH can be used in office practice provided patients are selected carefully and followed frequently and closely. Strict observation of criteria for selection of patients limited the size of the series of patients reported upon, but by the same token the incidence of complications from therapy was exceptionally small. Every physician who elects to employ these potent hormones must become familiar with their physiological effects and with the various methods of exhibiting them. Some of these effects are noted in this paper, but the experiences reviewed here provide an incomplete picture of the wide application of cortisone and ACTH.

EVERYONE is familiar with the discovery of the therapeutic effects of adrenocorticotropic hormone (ACTH) and of cortisone by Hench and coworkers.[3] Two years of clinical application of these hormones can be summarized in a general way:

1. These agents can provide palliation of uncomfortable and damaging effects of many non-endocrine diseases. The basis for the action of these drugs in such diseases appears to be pharmacodynamic rather than humoral.

2. In a disease of brief duration, such as certain drug sensitivity reactions or an isolated attack of uveitis or of rheumatic fever, the clinical manifestations can often be subdued until the process has run its course and therapy can be stopped safely.

3. Undesirable physiologic effects of large doses of adrenal steroids often appear, and, therefore, the problem of prolonged therapy may become extremely complicated. In many instances, however, doses of either hormone sufficient to provide a desirable therapeutic effect produce no undesirable effects, and prolonged therapy is possible.

4. Upon withdrawal of the drugs, clinical manifestations of chronic active disease return, usually with intensity comparable to that preceding therapy. Fortunately, undesirable "toxic" responses regress or disappear upon cessation of therapy.

5. Specific contraindications to use of these agents have been delineated.

For a little more than a year both ACTH and cortisone have been used by the authors in treating a series of carefully selected patients with a variety of diseases (Table 1).

Patients with acute, serious illness of brief duration were treated after only preliminary investigation for possible contraindications to therapy. Patients with chronic disease or diseases for which therapy was to be on a trial basis were carefully screened for presence of renal or cardiac insufficiency, hypertension, diabetes, mental disease, active tuberculosis, and history of peptic ulcer. The occurrence of any of these during therapy was watched for with great care in the clinic and in the laboratory. To prevent undesirable retention of large amounts of sodium and water, diets containing 2

TABLE 1.—*Data on Patients Treated with Cortisone and with ACTH in the Period April 1950 to April 1951*

Disease	Result: Success	Result: Failure	Treated at: Hospital	Treated at: Office, Home
TREATED WITH CORTISONE				
Rheumatoid arthritis	11	0	2	9
Rheumatic fever	1	0	1	0
Acute bursitis	3	0	0	3
Calcific bursitis, chronic	0	1	0	1
Gout, acute	1	0	0	1
Chronic	1	0	0	1
Asthma	4	4*	4	8
Atopic dermatitis	3	0	0	3
Drug sensitivity reactions	5	0	5	0
Eye disease:				
Uveitis (including post-traumatic)	13	2	2	13
Keratitis	4	2	0	6
Optic neuritis (all types)	3	3	5	5
Thyroiditis, acute	1	0	0	1
Pulmonary beryllosis	1	0	0	1
TREATED WITH ACTH				
Intramuscular administration:				
Asthma, acute status	2	0	2	0
†Collagen disease	1	0	1	0
Chronic ulcerative colitis	1	0	1	0
Pulmonary beryllosis	1	0	0	1
Gout	1	1	0	2
Pericarditis, tuberculous	0	1	1	0
Psoriasis with arthritis	1	0	0	1
Intravenous administration:				
Asthma, acute status	3	0	2	2
Discoid lupus erythematosus	1	0	0	1
Chronic hepatitis in acute exacerbation	1	0	1	0
†Collagen disease	1	0	1	0

* Improved initially, but had relapse while on treatment.
† Same patient.

Presented as part of a symposium on Cortisone and ACTH before the Sections on General Medicine and General Practice at the 80th Annual Meeting of the California Medical Association, May 13-16, 1951, Los Angeles.

gm. or less of sodium chloride were prescribed. Potassium citrate in doses of 3 to 9 gm. (25 to 75 mEq.) a day was given to maintain potassium balance and to prevent, if possible, unusual nitrogen loss. Eosinophil counts were done periodically during the use of both hormones; although found useful in judging therapy with ACTH, they were abandoned in cortisone-treated patients.

TREATMENT WITH CORTISONE

During the first three months cortisone was used in the work here reported, it was given intramuscularly, usually in doses of 200 to 300 mg. the first day or two, and 100 mg. daily thereafter. From July 1950, the suspension was given orally to all patients who could accept oral therapy, first in syrup and later, when available, in tablet form. The daily oral dose was divided into four or three doses given at five-hour to eight-hour intervals during the waking hours. Oral doses of cortisone usually totalled 200 mg. the first day, followed by 100 mg. daily thereafter until the desired clinical effect was assured. The daily dose was then reduced by 12.5 mg., maintained at the new level for several days, then reduced another 12.5 mg. and so on until the minimal effective dose was ascertained. Rarely a patient would require more than 100 mg. daily to produce a therapeutic effect. In no instance was it necessary to use more than 150 mg. daily, although it is recognized that larger doses may be required for some patients. Doses of 75 to 100 mg. were usually necessary to control clinical manifestations of disease; only one patient with chronic gout required less. Withdrawal of cortisone after three to four weeks of therapy was accomplished by diminishing the dose by 25 mg. every three to four days. With this schedule of therapy no signs of post-cortisone adrenocortical hypofunction were noted.

Rheumatoid Arthritis: The experience with cortisone in this disease was similar to that recorded elsewhere. Eleven patients were treated with doses of 75 to 100 mg. daily for over four months with no evidence of "toxicity" or of development of adrenal atrophy. Two patients did not benefit sufficiently to warrant continuous therapy. In one case mild hypertension developed, and when edema also developed despite careful salt restriction, use of the drug was discontinued.

Rheumatic Fever: One patient, a girl aged 11 with acute rheumatic fever and carditis, was treated with cortisone. Within the first 24 hours, while receiving 200 mg. of cortisone orally, she became afebrile, an aortic diastolic murmur disappeared, and the electrocardiogram returned to normal. An apical diastolic murmur was unchanged. The patient received 100 mg. daily for four days, then 87.5 mg. for four days and finally 75 mg. daily for a total of 28 days followed by gradual reduction of dose without recurrence of acute disease. It is too early to assess the effect of the drug on development of valvular disease. For this patient rheumatic fever was, for the most part, an asymptomatic rest in bed.

Acute Bursitis: On the suggestion of Engleman,[1] cortisone was used to treat one case each of acute subdeltoid bursitis, tennis elbow and subgluteal bursitis. A total dose of 1 gm. (200 mg. the first day, followed by 100 mg. a day for eight days) provided early remission of pain and return of motion in three patients. In a fourth patient with chronic calcific subdeltoid bursitis, treatment was unsuccessful.

Gout: One patient, aged 64, with chronic tophaceous gout of many years' duration was treated with cortisone, 50 mg. daily for 42 days, with complete relief. At last report he had been without therapy of any kind for eight weeks and remained well. Deformity from tophi and damaged joints was not altered, but the patient recovered from a totally disabled state to the point where he could attend his office and play golf. A second patient was treated for an acute, severe attack of gout that was unaltered by colchicine. He was given 200 mg. daily the first three days, followed by 150 mg. daily for five days with complete recovery. Colchicine, 0.6 mg. four times daily, was added after relief from cortisone had been obtained. A recurrence a month later was treated with ACTH.

Asthma: Eight patients with severe, chronic asthma were treated either for acute, threatening attacks of asthma or for chronic respiratory embarrassment that would not yield to proper conventional treatment even in the hospital. Four had fair response to cortisone in doses of 100 to 150 mg. per day, but received no benefit from smaller doses; treatment was abandoned in these patients. The other four responded remarkably well and have received intermittent therapy since then. One of them has had remissions of four to six weeks after each course of treatment, in contrast to a previous state of continuous asthma. Cortisone certainly is of value in the treatment of asthma, but failures are common and the problems of continuous therapy always present.

Atopic Dermatitis: Three patients with atopic dermatitis were treated for periods of two to six weeks with rapid and complete clearing of skin lesions. All had relapse within a few weeks after therapy was stopped, but in each case the relapse was not so severe as the previous disease.

Drug Sensitization: Four patients with serious sensitivity reactions to penicillin and one with a reaction to streptomycin received cortisone orally. All responded rapidly to an initial dose of 200 mg. the first day followed by 100 mg. daily for seven to ten days. Fever, exfoliation, erythema bullosum-like lesions, and edema cleared within 48 hours. The usually severe "toxic" course of such reactions can be reduced to a mild reaction that allows for rapid recovery once the offending agent has been removed or excreted.

Eye Disease: Twenty-seven patients were treated (Table 2). Fifteen of them had uveal tract disease (chorioiditis or iritis), and four of the patients in this group were treated only with eye drops of cortisone suspension in a concentration of either 2.5

per cent or 0.8 per cent. The drops were instilled hourly during waking hours for the first seven to 14 days, after which the interval was lengthened periodically until a maximum of four times a day was reached. At night an ophthalmic ointment (2.5 per cent cortisone) was used. Three of the four patients improved remarkably; one, only slightly. With cessation of therapy there was recurrence of clinical evidence of disease in three patients, but resumption of treatment controlled inflammatory signs until the disease had run its course and treatment could be stopped. In the ordinary case, three to six weeks of treatment was required. Local therapy alone may often induce rapid disappearance of keratitic precipitate, of vascular engorgement, of vitreous opacities and even of chorioidal lesions. Five patients not suited for oral treatment or local instillation of drops were given 0.5 cc. of the standard suspension of cortisone subconjunctivally every two to three weeks for three doses with rapid healing of acute, severe chorioiditis. Two patients with acute chorioiditis had prompt healing with use

TABLE 2.—*Treatment of Diseases of the Eye with Cortisone*

Diagnosis	Dose and Method of Administration	Response
Iridocyclitis, acute, bilateral	Intramuscular 2.1 gm. in 10 days	Rapid cure
Iridocyclitis, chronic, bilateral with rheumatoid arthritis	Oral 100 mg. daily continuously	Rapid improvement while on treatment
Chorioiditis, chronic, severe, 1 yr.	Intramuscular 100 mg. daily, 2 mo.; 300 mg. weekly 1 mo.	Marked improvement (cure?); all other treatment failed
Chorioiditis, chronic, severe	Intramuscular 100 mg. to 150 mg. daily	Exacerbation on 150 mg.; treatment stopped
Uveitis, chronic, with secondary glaucoma	Subconjunctival 0.5 cc. (12.5 mg.) every 3 wk. three times	Remarkable improvement; well with no treatment, 4 mo.
Chorioiditis, acute, severe	Subconjunctival 0.5 cc. (12.5 mg.) every 3 wk. three times	Remarkable improvement; healed 6 wk.
Iridocyclitis, post-traumatic	Subconjunctival 0.5 cc. twice	Cleared very rapidly
Iridocyclitis, post-traumatic	Subconjunctival 0.5 cc.	Rapid clearing of lesion
Vitreous hemorrhage, postoperative, 8 wk. duration	Subconjunctival 0.5 cc.; given deep, episcleral	Pronounced clearing in 5 days
Glaucoma, acute, secondary to iridocyclitis. (Due to histoplasmosis sensitivity?)	Eye drops (2.5%) every hr.; subconjunctival 0.5 cc.	Prompt and complete reversal of disease
Chorioiditis, acute, recurrent	Eye drops (2.5%) every hr.; subconjunctival 0.5 cc. every 2 wk. 4 times.	Slow, steady improvement; almost healed
Iridocyclitis, post-traumatic	Eye drops (2.5%) every hr.	Rapid recovery
Iridocyclitis, acute	Eye drops (0.8%) every hr.	Moderately good result
Iridocyclitis and keratitis, post herpes zoster	Eye drops (2.5%) every hr.	Good response with healing
Iridocyclitis, recurrent	Eye drops (0.8%) every hr.	Fair to no effect
Keratitis, severe (etiol?)	Eye drops (2.5%) every hr. for 3 wk.	Good response; little or no scar
Keratitis, bilateral, allergic	Eye drops (2.5%) every hr.; ointment (2.5%) at night	Excellent response
Keratitis, recurrent, (etiol?)	Eye drops (0.8%) every hr.	Rapid improvement
Keratitis, postoperative	Eye drops (2.5%) every hr.	Fair response, healing incomplete
Keratitis, dendritic, acute	Eye drops (2.5%) every 2 hr.; subconjunctival 0.5 cc. weekly	Symptomatic improvement; slow healing
Conjunctivitis, chronic; keratitis sicca, healed	Eye drops (0.8%)	Subjective improvement
Retrobulbar neuritis, acute	Intramuscular or oral 100 mg. daily for 20 days	Rapid improvement to 20/20 vision
Retrobulbar neuritis	Intramuscular 300 mg. daily for 2 days; 100 mg. daily for 14 days	Slow improvement to normal vision
Optic neuritis and neuroretinitis, bilateral, severe	Oral 100 mg. daily	Rapid improvement in 4 days; had not improved in 10 days prior to treatment
Retrobulbar neuritis	Oral 100 mg. daily for 14 days	Failure
Optic neuritis and papillitis, severe	Oral 100 mg. daily for 28 days; subconjunctival 12.5 mg.	Failure
Optic neuritis, acute; tenosynovitis, external rectus	Oral 100 mg. daily for 21 days; eye drops (2.5%) every hr.; ACTH 20 mg. intravenously daily for 3 days after cortisone treatment	Failure to all therapy; ACTH inadequate

of eye drops and subconjunctival injection. Of four patients treated with cortisone orally or intramuscularly in conventional manner, three had excellent response and one had recurrence of disease while still receiving the hormone.

Four patients with keratitis were treated successfully with cortisone eye drops; two others had little or no improvement on local or subconjunctival therapy.

Six patients received cortisone orally or intramuscularly for optic neuritis or retrobulbar neuritis. Only three improved while on cortisone; the other three were not helped.

Thyroiditis: A 52-year-old female with acute thyroiditis of two weeks' duration was given cortisone, 100 mg. daily for 10 days. After 36 hours of treatment the gland, which had been enlarged and very tender, was no longer painful and the temperature became normal. The thyroid gland diminished only slightly in size, but became firm. No complication such as dysthyroidism or dysphagia developed.

GENERAL OBSERVATIONS

Nineteen patients acutely ill with drug sensitivity reactions, severe rheumatoid arthritis, serious eye disease, and status asthmaticus were started on treatment in the hospital only because their condition was serious enough to justify hospitalization. Therapy was initiated in the office or home on an ambulatory basis in 27 patients treated with cortisone orally or parenterally, and in 17 patients with ophthalmic disease treated by local application of cortisone suspension. Patients were observed daily during the initial week of therapy and at less frequent intervals as treatment was prolonged. All patients were observed at least once a week for check on mental state, weight, blood pressure and glucose in the urine.

Treatment had to be stopped in only two cases because of undesirable reactions. In one case hyperglycemia with glycosuria and acetonuria developed. As cortisone had provided only minimal relief from asthma, cessation of therapy was acceptable to the patient. Acute rise of blood pressure to serious hypertensive levels prompted cessation of therapy in a patient with rheumatoid arthritis.

In one patient with rheumatoid arthritis and a decrease in glucose tolerance determined prior to treatment, mild hyperglycemia and persistent 1 to 2 plus glycosuria developed during maintenance on 100 mg. cortisone daily. At last report the patient had been under treatment for four months with satisfactory improvement in arthritis and no advance of the "steroid diabetes."

TREATMENT WITH ACTH

Because ACTH must be administered parenterally, only a few patients were treated with it prior to a few months ago. The basis for selection of patients was identical to that for cortisone therapy.

Diagnostic test for adrenal function: Eight patients were tested according to the method of Thorn, with a decrease in eosinophils in the blood the sole criterion. Often, the recommended dose of 25 mg. of ACTH intramuscularly did not produce a 50 per cent decrease in eosinophils in normal persons; a dose of 40 to 50 mg. was required.

Asthma: Two patients with status asthmaticus responded favorably within six to 12 hours to ACTH, 25 mg. intramuscularly every six hours. Therapy was stopped when the acute attack had completely subsided, usually in four to seven days.

Pericarditis: A 22-year-old student was treated for what was thought to be rheumatic fever with pericarditis. He received 25 mg. of ACTH intramuscularly every six hours. Fever disappeared, tachycardia diminished, but the pericardial rub persisted. Pericardiocentesis was done and sanguinous fluid was withdrawn. No organisms were grown on culture of the fluid. After five days fever returned and it was then concluded that the most likely etiologic factor was M. tuberculosis. ACTH was stopped and appropriate therapy instituted. There is no evidence that this brief exposure to ACTH was harmful; of interest was the rapid alleviation of pain, fever and tachycardia with persistence of the active disease.

Pulmonary Beryllosis: A 36-year-old neon sign worker with chronic pulmonary granulomatosis resulting from working with beryllium was treated with ACTH, 100 mg. intramuscularly daily, with rapid decrease in dyspnea, moderate increases in vital capacity from 2,800 cc. to 3,600 cc., and increased capacity for exercise. Appetite improved and there was a gain of 16 pounds in body weight. While the patient was being maintained on 30 to 40 mg. daily for eight weeks, there was gradual reversion to the pretreatment state of pulmonary insufficiency. An increase in dose was not thought to be safe in this patient. He did poorly when without treatment. Cortisone, 100 mg. daily, produced satisfactory improvement—almost comparable to the best state while on ACTH. The patient was maintained on cortisone for three months without incident. Use of the drug was then discontinued and at the time of last report the patient had been more comfortable for three months than at any previous time when not being treated. It is planned to continue with ACTH or cortisone in courses interspersed with rest periods.

Gout: Two patients had relief from acute attacks of gout following a single dose of 50 mg. of ACTH intramuscularly. Both were treated with colchicine, 0.5 mg. three times daily, in the hope that recurrence would be prevented. Another patient had no response to one dose of ACTH, 50 mg. intramuscularly. At the time of this report he was being studied further with larger doses.

Chronic Ulcerative Colitis: A 38-year-old female was treated with ACTH after four months of severe, acute exacerbation of chronic ulcerative colitis. The dosage was at the rate of 100 mg. daily for two and one-half days, then 80 mg. daily for two days, and

60 mg. daily for two days. Each day's dose was divided into four equal doses given six hours apart. The patient became afebrile in 24 hours. Vomiting ceased and diarrhea improved. After completion of this brief course of therapy the patient had only six or seven defecations a day instead of the 20 to 30 a day previously. After ten days of relative well-being, relapse occurred. It was recognized that so brief a course of ACTH therapy would not insure a lasting remission, but continued administration was impossible for financial reasons. The prompt response to ACTH in this case indicates that this agent offers advantage in the treatment of devastating exacerbations of ulcerative colitis and of regional enteritis.

INTRAVENOUS ADMINISTRATION OF ACTH

Following Gordon's report[2] at the second ACTH Conference, ACTH was given intravenously to a selected group of patients.* It has been confirmed that ACTH can be given safely intravenously. Great therapeutic effect results from doses of 10 to 25 mg. dissolved in 5 per cent glucose and given over a period of four to 16 hours. The longer the time of the infusion, the greater the physiologic response on the part of the adrenal cortex; the effect of a dose given intravenously may be equal to a daily intramuscular dose five to ten times greater.[2, 4] It is of great importance to prevent potassium depletion in patients given the substance intravenously. In the present series 25 to 50 mEq. of potassium (3 to 6 gm. potassium citrate) was given daily to all patients who received ACTH intravenously.

Test for adrenal insufficiency: A patient with asthma who had received cortisone, 100 mg. daily for six weeks, followed by two months of conservative therapy, had a severe, unremitting attack of asthma. In a routine Thorn test there was no decrease in eosinophils. A test with ACTH, 25 mg. given intravenously as a drip for four hours, produced a change in eosinophil count from 1,430 per cu. mm. to 123 per cu. mm. six hours after start of the infusion. The patient received the hormone intravenously daily for three days with complete relief from the attack.

Asthma: Three patients with severe, acute attacks of asthma were treated with 10 to 25 mg. of ACTH intravenously daily or every other day for three to six doses with excellent results. Two were treated in the hospital. One patient was treated in the office with 25 mg. in 500 cc. of 5 per cent dextrose in water given over a three- to four-hour period every other day.

Discoid lupus erythmatosus: A 27-year-old woman was treated with ACTH, 10 mg. every other day, given intravenously with infusion taking three to four hours. The patient became afebrile, and the generalized skin lesions rapidly regressed. Seven doses were given without appearance of undesirable effects. Relapse occurred after cessation of therapy, and the patient was given 10 mg. three times weekly for another four doses with excellent results. At last report, five weeks later, there was no relapse.

Chronic hepatitis in acute exacerbation: A 35-year-old woman who had an acute bout of virus hepatitis in October 1950, had a relapse late in November. She improved slowly and by February 1951 was considered to be almost well. In March she again became jaundiced, and because of fever, anorexia, intense jaundice and a greatly enlarged liver (the lower margin at the iliac crest) was placed in the hospital. Results of laboratory studies were indicative of seriously impaired liver function. The patient was not improved after ten days of rest and usual care. ACTH, 10 mg. daily in 1,000 cc. of 5 per cent dextrose in water, given intravenously over 12 hours, was begun on a trial basis. Within 48 hours the patient was afebrile and eating heartily. After five doses, the drug was withheld for one day, and the patient again was ill, febrile (102° F.) and could not eat. Next day, after receiving 5 mg. of ACTH intravenously in six hours she was again afebrile and had begun to eat. The improvement, clinically and by liver function appraisal, was remarkable while the daily infusions of 10 mg. ACTH were continued. After a total of 23 days of treatment, ACTH was stopped. At last report, three weeks later, improvement was continuing. It is likely that ACTH so suppressed the toxic, febrile manifestations of hepatitis that the patient was able to eat and to effect some sort of hepatic protective mechanism more readily.

Collagen disease: A 71-year-old male successfully treated with cortisone had relapse when cortisone was withdrawn. Four weeks later, in April 1951, exacerbation of rheumatoid disease occurred. With this there developed extensive involvement of synovia, pleura, pericardium, and skin, associated with fever and extreme debility. ACTH was given, 100 mg. daily intramuscularly, with rapid improvement. Reduction of the dose to 60 mg. daily was followed by exacerbation of disease. The patient was given ACTH, 25 mg. daily intravenously, with rapid improvement. At last report he had been maintained on ACTH intravenously daily for ten days — the dose then was 20 mg. daily—and was much improved objectively and subjectively.

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* This work was done in collaboration with E. P. Engleman, M.D.

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